AD-A193 881 ATROPINE STRESS AND HUMAN PERFORMANCE(U) OKLAHOMA UNIV 1/1
HEALTH SCIENCES CENTER OKLAHOMA CITY
H L WILLIAMS ET AL. JAN 87 DAMD17-83-C-3194

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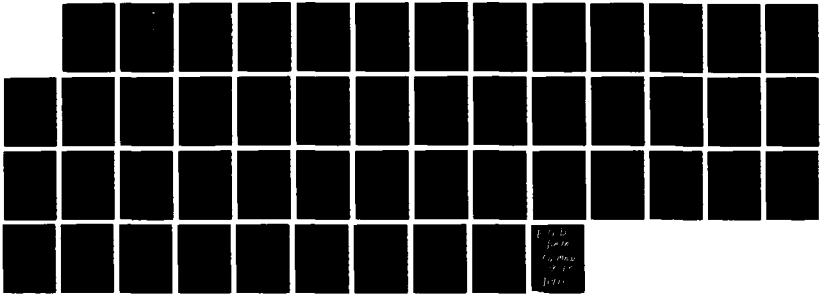

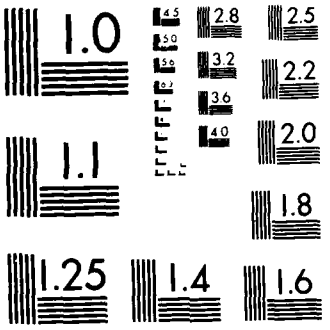

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ATROPINE, STRESS AND HUMAN PERFORMANCE

ANNUAL REPORT

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Harold L. Williams
John Carney
Frank A. Holloway

January 1987

Supported by
U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701-5012

Contract No. DAMD17-83-C-3194

The University of Oklahoma Health Sciences Center
P.O. Box 26901
Oklahoma City, Oklahoma 73190

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SECURITY CLASSIFICATION OF THIS PAGE

REPORT DOCUMENTATION PAGE

Form Approved OMB No. 0704-0188

1a. REPORT SECURITY CLASSIFICATION: Unclassified	1b. RESTRICTIVE MARKINGS
2a. SECURITY CLASSIFICATION AUTHORITY	3. DISTRIBUTION/AVAILABILITY OF REPORT: Approved for public release; distribution unlimited
2b. DECLASSIFICATION/DOWNGRADING SCHEDULE	
4. PERFORMING ORGANIZATION REPORT NUMBER(S)	5. MONITORING ORGANIZATION REPORT NUMBER(S)
6a. NAME OF PERFORMING ORGANIZATION: University of Oklahoma Health Sciences Center; 6b. OFFICE SYMBOL (If applicable)	7a. NAME OF MONITORING ORGANIZATION
6c. ADDRESS (City, State, and ZIP Code): P.O. Box 26901, Oklahoma City, OK 73190	7b. ADDRESS (City, State, and ZIP Code)
8a. NAME OF FUNDING/SPONSORING ORGANIZATION: U.S. Army Medical Research & Development Command; 8b. OFFICE SYMBOL (If applicable)	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER: DAMD17-83-C-3194
8c. ADDRESS (City, State, and ZIP Code): Fort Detrick, Frederick, Maryland 21701-5012	10. SOURCE OF FUNDING NUMBERS: PROGRAM ELEMENT NO. 63764A; PROJECT NO. 3M4-63764D995; TASK NO. AA; WORK UNIT ACCESSION NO. 012

11. TITLE (Include Security Classification)

Atropine, Stress and Human Performance

12. PERSONAL AUTHOR(S)

Harold L. Williams, Ph.D.; John Carney, Ph.D.; Frank A. Holloway, Ph.D.

13a. TYPE OF REPORT	13b. TIME COVERED	14. DATE OF REPORT (Year, Month, Day)	15. PAGE COUNT
Annual	FROM 85/9/30 TO 86/9/29	January 1987	51

16. SUPPLEMENTARY NOTATION

17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
FIELD	GROUP	SUB-GROUP	Atropine dose effects, Exercise, Information processing, Human performance, Heart rate, Pupil size, Stress
06	15		
06	01		

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

This study investigated the independent and combined effects of a 2.0 mg dose of atropine, a period of pre-dose exercise and a night of sleep loss on cognitive performance, self-reports, sleepiness and physiological variables in healthy young men. Recent studies suggested that both atropine and sleep deprivation cause selective impairment of cognitive functions associated with the active processing of information input. Carney's work with rodents suggested that exercise might potentiate the effects of subsequent doses of atropine. The results in Year 3 replicated those in Years 1 and 2 showing that atropine impairs input cognitive processing functions but not output functions in both visual and auditory information processing tasks. More specifically, atropine caused decreases in d' with no change in β in a visual aircraft identification task and an auditory vigilance task. In an oddity matching task, atropine effects interacted with those of stimulus quality but not with those of stimulus-response compatibility on choice reaction time. Confirming the results reported for Year 2, sleep loss also caused selective impairment of cognitive functions associated with input processing, leading to hyperadditive atropine-dose X sleep-state interaction effects on both response(back)

20. DISTRIBUTION/AVAILABILITY OF ABSTRACT	21. ABSTRACT SECURITY CLASSIFICATION
☐ UNCLASSIFIED/UNLIMITED ☒ SAME AS RPT. ☐ DTIC USERS	Unclassified

22a. NAME OF RESPONSIBLE INDIVIDUAL	22b TELEPHONE (Include Area Code)	22c. OFFICE SYMBOL
Mary Frances Bostian	(301)663-7325	SGRD-RMI-S

DD Form 1473, JUN 86 *Previous editions are obsolete.* SECURITY CLASSIFICATION OF THIS PAGE

Block 19 Abstract (cont.):

accuracy and speed. Carney's findings were not replicated in humans, Exercise had no significant main effect on performance and failed to potentiate the effects of atropine. However, exercise effects did interact with those of sleep deprivation, potentiating the deleterious effects of sleep loss on visual signal detection, auditory vigilance and choice reaction time. With both atropine dose and sleep loss, subjects reported decreases in alertness and efficiency. The multiple sleep latency test, introduced in Year 2, confirmed the self-report data on alertness. Both atropine and sleep loss caused increased sleepiness and their effects were interactive. Exercise did not afffect sleep tendency. As expected, the 2.0mg atropine dose caused pupillary dilation and large increases in heart rate. The tachycardia was accompanied by an increase in diastolic blood pressure. Exercise caused large increases in heart rate accompanied by increased systolic pressures with no change in diastolic pressure. There were no significant dose X exercise interaction effects on the cardiovascular measures. Sleep loss had no significant effects on any of the autonomic variables. In general, the data suggest that atropine and sleep loss in combination could lead to catastrophic performance failures in the field, particularly on tasks that demand accurate and high speed analysis of visual or auditory information. (KT)

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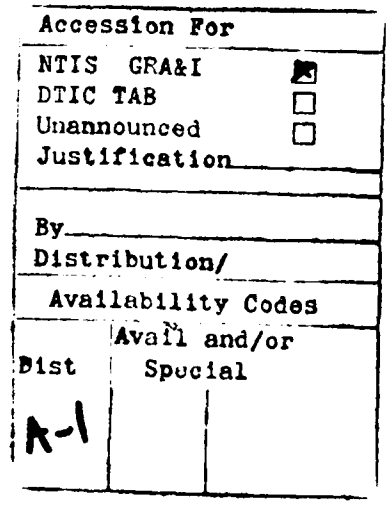

Supported by
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SUMMARY

This study investigated the independent and combined effects of a 2.0 mg dose of atropine, a period of pre-dose exercise and a night of sleep loss on cognitive performance,self-reports, sleepiness and physiological variables in healthy young men. Recent studies suggested that both atropine and sleep deprivation cause selective impairment of cognitive functions associated with the active processing of information input. Carney's work with rodents suggested that exercise might potentiate the effects of subsequent doses of atropine. The results in Year 3 replicated those in Years 1 and 2 showing that atropine impairs input cognitive processing functions but not output functions in both visual and auditory information processing tasks. More specifically, atropine caused decreases in d' with no change in ß in a visual aircraft identification task and an auditory vigilance task. In an oddity matching task, atropine effects interacted with those of stimulus quality but not with those of stimulus-response compatibility on choice reaction time. Confirming the results reported for Year 2, sleep loss also caused selective impairment of cognitive functions associated with input processing, leading to hyperadditive atropine-dose x sleep-state interaction effects on both response accuracy and speed. Carney's findings were not replicated in humans. Exercise had no significant main effect on performance and failed to potentiate the effects of atropine. However, exercise effects did interact with those of sleep deprivation, potentiating the deleterious effects of sleep loss on visual signal detection, auditory vigilance and choice reaction time. With both atropine dose and sleep loss, subjects reported decreases in alertness and efficiency. The multiple sleep latency test, introduced in Year 2, confirmed the self-report data on alertness. Both atropine and sleep loss caused increased sleepiness and their effects were interactive. Exercise did not affect sleep tendency. As expected, the 2.0 mg atropine dose caused pupillary dilation and large increases in heart rate. The tachycardia was accompanied by an increase in diastolic blood pressure. Exercise caused large increases in heart rate accompanied by increased systolic pressures with no change in diastolic pressure. There were no significant dose x exercise interaction effects on the cardiovascular measures. Sleep loss had no significant effects on any of the autonomic variables. In general, the data suggest that atropine and sleep loss in combination could lead to catastrophic performance failures in the field, particularly on tasks that demand accurate and high speed analysis of visual or auditory information.

FOREWORD

For the protection of human subjects, the investigators have adhered to policies of applicable Federal Law 45CFR46.

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1. Statement of the Problem

The overall aims of this research program are to investigate dose effects of atropine alone and combined with such stress-related variables as sleep deprivation and pre-dose exercise on cognitive performance and psychophysiology of healthy young male volunteers. The specific aims of the third year of work were to investigate the independent and combined effects of three experimental treatments on the performance of cognitive tasks and on selected physiological variables including somnographic measures of daytime sleepiness, as defined by a multiple sleep latency test. The three treatments were: (1) a single intramuscular 2.0 mg dose of atropine sulfate; (2) one night of sleep deprivation, and (3) moderate pre-dose exercise. The cognitive tasks were first selected and developed by two criteria: (1) Their apparent validity for certain information-processing requirements likely to be encountered in contemporary military jobs, and (2) their probable sensitivity to anticholinergic compounds, sleep loss and exercise. Task modifications made in Year 2 and continued in Year 3 permitted more refined analyses of the selective effects of atropine, sleep loss, and exercise on input (perceptual) and output (response-related) components of information processing.

The dose-related effects of atropine on most of the physiological variables selected for this research are rather well documented (1, 2, 3, 4), but there are no studies of these effects in combination with sleep deprivation or pre-dose exercise, nor are there any studies of the independent or combined effects of these treatments on sleepiness as assessed by the multiple sleep latency test (5).

2. Rationale

The research literature indicates that relatively small doses of atropine may impair cognitive functions that are essential components of a number of military field jobs (4, 6). One night of sleep loss also causes impairment on tasks that probably have military relevance (e.g., 7, 8, 9), and the dose effects of atropine may interact with those of sleep deprivation, producing synergistic effects on performance. Our selection of pre-dose exercise for study as a second stress-related variable was based on investigations by Carney et al. (10) in rodents. They found that when rats were given moderate pre-dose exercise on a treadmill, atropine dose effects on schedule-controlled operant behavior were potentiated. It is important to determine whether the three treatments, atropine, sleep deprivation and pre-dose exercise, have additive or hyperadditive (interactive) effects on human performance.

3. Background and Literature Review

a. Dose effects of atropine on information processing, self reports and selected physiological variables.

a.1 Information processing

Most studies of the effects of cholinergic drugs on cognitive and psychomotor functions have been task focused and empirical (see 4 for a review). Typically, such research employs a battery of performance tasks, each of which challenges a variety of skills. Although the test score profiles may differ systematically for different treatments (e.g., different drugs), precise conclusions about which cognitive functions are differentially affected by a given treatment are difficult make. The tasks used in such studies usually lack a theoretical rationale, and the skill components represented in the tasks are often too complexly organized for valid functional analysis. For the first year of the present contract, the protocols of this research program were also primarily empirical and task oriented. However, the findings from that year, considered with some relatively recent results and theoretical concepts from other investigators, led to hypotheses about specific functional impairments likely to be observed with a moderate dose of atropine, and then to appropriate modifications of our laboratory tasks.

In his 1977 review, Warburton (11) concluded that the ascending cholinergic reticular pathways are involved primarily in the recognition and selection of environmental stimuli and not in the selection, organization or execution of responses. Evidence for this hypothesis came first from animal studies in which cholinergic agonists such as physostigmine improved stimulus detection performance (12), while cholinolytics such as scopolamine disrupted stimulus detection performance (13). Statistical analyses of their data, based on Signal Detection Theory (14), showed that these changes in stimulus detection performance resulted from drug-induced alterations in perceptual sensitivity (d') rather than in alterations in criteria for responding or in willingness to respond (ß). Warburton and his colleagues concluded that central muscarinic cholinergic blockade disrupts signal detection performance by causing specific impairment of perceptual sensitivity. Later, Wesnes and Warburton (15) showed that two compounds, scopolamine and nicotine, which have opposite effects on central cholinergic functions, produced opposite effects on visual signal detection in a high-speed information-processing task.

Calloway(16) employed a serial stage,information-processing, theoretical model of choice reaction time along with Sternberg's (17) additive factor method to investigate the effects of several psychotropic chemicals on human performance. Using event-related brain potentials elicited by stimuli within information-processing tasks, Calloway produced results that agreed with those of Warburton and his colleagues in that scopolamine impaired input processes associated with stimulus encoding, but not output processes such as those associated with response selection and response execution. More recently, Dunne and Hartley (18) concluded that the effects of scopolamine on retention were due to modulation of selective attention rather than of memory functions per se. They suggested that the cholinergic system may be cen-

trally involved in the control of effortful or intentional information processing and that cholinergic blockade acts to reduce the degree of control that the organism has over a particular effortful function, the selection of task-relevant information. The dichotomy between stimulus processing and response processing suggested by these investigations matches the functional distinction between cholinergic and aminergic neurochemical systems noted by others. For example, Vanderwolf and Robinson (19) suggest that there are two different kinds of input from the reticular activating system to the hippocampus and cerebral cortex. One input system appears to be cholinergic and may have an important role in selective attention and stimulus identification. The second input is probably aminergic and appears to be related to motor functioning.

In the first year of work on the present project, during which we investigated dose effects of atropine administered alone and in combination with moderate pre-dose exercise, some of our performance tasks placed relatively greater emphasis on perceptual functions such as stimulus identification, whereas other tasks put greater emphasis on output functions such as response preparation and motor control As could have been predicted from the research cited above, the tasks that proved to be most sensitive to the dose effects of atropine (up to 2.0 mg) were those that emphasized perceptual functions. One such task required the subject to distinguish "friendly" from "enemy" aircraft silhouettes that differed slightly in shape. Failure to identify and destroy the enemy target within 700 msec of target onset resulted in a mildly aversive white flash. False alarms (shooting down friendly aircraft) resulted in a rather unpleasant buzz. Bonus points, convertible to cash, could be accumulated for fast and accurate responses. Statistical analyses of the signal detection data revealed systematic atropine dose effects on both hits and false alarms, resulting in a dose-related reduction in d' with no drug effect on the "caution" statistic, ß. We concurred with Warburton and colleagues that muscarinic cholinergic antagonists impair signal detection by decreasing d' and not by altering ß.

Atropine administered alone had no dose effect on a different task, interval estimation. However when pre-dose exercise was added to the protocol, interval estimation errors increased systematically with atropine dose. The interval estimation task does have an important motor component because nearly all subjects try to maintain accurate estimation by rhythmic movements of the hands or feet. Except for the latter finding, our results in the first year were generally consistent with the hypothesis put forth by Wesnes and Warburton (12) and by Calloway (16) that antimuscarinic agents cause selective impairment of input perceptual functions such as stimulus identification rather than of output motor functions such as response selection and execution.

In the second year of this project, during which we investigated the effects of atropine (2.0 mg) independently and in combination with a night without sleep, there were three subtests in

the performance battery--visual aircraft identification, auditory vigilance and oddity matching. The aircraft identification task required the subject to discriminate between two equally probable aircraft silhouettes that emerged gradually from a visual noise background. The subjects were instructed to shoot down enemy aircraft but preserve friendly aircraft. The major dependent variables were hits, false alarms, d' and ß. In the auditory vigilance task, the subject heard a randomly ordered series of tone pips composed of five different pitches, the lowest of which was designated the target tone. The subject was to press a button as quickly as possible to the target tone and withhold responses to nontargets. The response variables of principal interest were again d', ß, hits and false alarms.

In the oddity-matching reaction time task, the subject was presented with a series of displays, each composed of four dials arranged in a square. The four response buttons were also arranged in a square with a "hold" button in the center. Each dial contained a pointer, one of which was oriented in a different direction from the other three. The subject was instructed to identify the odd pointer, lift his finger from the hold button and press the designated button as quickly as possible. Reaction time was the time between display onset and release of the hold button; motor time was the time between release of the hold button and response on the designated button. Accuracy was also measured but was kept relatively constant, above 93%, by instructions and feedback. There were three orthogonally programmed task variables, display quality (DSQ), stimulus-response compatibility (SRC) and time uncertainty (TU), each targeted on a different hypothetical stage of the reaction process.

The Year 2 results for atropine alone were similar to those of Year 1. In the aircraft identification task, the 2.0 mg dose of atropine reduced d' but had no effect on ß. Neither the auditory vigilance task nor the oddity-matching task proved to be quite as sensitive as the aircraft identification task to the 2.0 mg dose of atropine. For the auditory task, the effect of atropine dose on hits, false alarms and d' became statistically significant only in the sleep-deprived state. For the oddity-matching task, the atropine dose caused significant slowing of reaction time only when performance had already been degraded either by low DSQ or by sleep deprivation. The significant dose by DSQ interaction effect was interpreted as further evidence that atropine impairs functions associated with stimulus identification.

Taken together, our findings with atropine continue to be consistent with Warburton's (11) view that muscarinic cholinergic blockade produces an impairment of perceptual functions associated with stimulus identification. Depending on such task characteristics as speed/accuracy instructions and feedback to the subject, these effects may be observed either as loss of accuracy or slowing of response speed.

a.2 Self reports

In the Year 1 studies, with increasing atropine dose, the subjects reported feeling more sleepy and weary, less efficient, more confused, and slower and less steady. At the 2.0 mg dose, some of the subjects also reported blurred vision and a sense of dryness. Most of the same atropine dose effects were found in Year 2. These findings are consistent with self-assessment data reported by Nuotto (20).

a.3 Physiological variables

In Year 1, as expected from studies by others (e.g., 21), heart rate proved to be quite sensitive to atropine dose, showing a decrease following the lowest dose (0.5 mg) and a considerable increase following each of the higher doses. Pupillary diameter also increased with atropine but only at the highest dose (2.0 mg). Skin conductance decreased with atropine dose.

In Year 2, measures were added to the physiological battery. Blood pressure has usually not been sensitive to a 2.0 mg dose of atropine, at least in healthy subjects (22). As expected, mean systolic pressures showed no systematic change with increasing atropine dose. However, diastolic pressure did show a small but statistically significant increase following 2.0 mg of atropine. We will withhold interpretation of these results pending cross-validation in Year 3.

In Year 2, we introduced the multiple sleep latency test which has proved to be an extremely sensitive index of sleepiness (e.g., 5). Since, as reported above, subjects do complain of drowsiness, reduced alertness and fatigue following atropine injection, it is of interest to know whether a direct measure of sleepiness (sleep tendency) is sensitive to atropine effects. The results in Year 2 were consistent with the self-report data in that 2.0 mg of atropine caused an increase in sleepiness which registered as a decrease in sleep latency, confirming the self reports of drowsiness and reduced alertness.

b. Effects of moderate exercise on information processing, self reports and selected physiological variables.

b.1 Information processing

Studies that have used exercise interventions to investigate the effects of physical arousal on cognitive functioning have produced conflicting findings (see 23 for a review). Some researchers have reported that exercise facilitates cognitive abilities both during and after physical exertion, whereas others have reported that exercise impairs mental functioning. To complete the picture, some investigators have found no effects of exercise on cognition. Tomporowski and Ellis (23) suggest that these conflicting findings may be related to the physical fitness of the subjects tested. There is consistent evidence that physi-

cally fit subjects perform cognitive tasks better after exercise that less fit subjects. In general, however, the evidence suggests that the effects of exercise on cognitive functioning are indirect rather than direct, mediated by motivational variables and subject expectancies.

Recent studies by Carney et al. (10) showed that pre-dose exercise administered to rats could potentiate the dose effects of atropine on schedule-controlled operant behavior, and there is some evidence for similar synergistic effects in humans (24). However, in our Year 1 studies, exercise alone had no significant effects on task performance and there was no firm evidence favoring the hypothesis that exercise can enhance the potency of a subsequent dose of atropine. Performance on the interval estimation task did show an atropine dose effect only after moderate exercise, but the dose x exercise interaction effect was not statistically significant.

b.2 Self reports

In our Year 1 investigation, moderate exercise tended to reverse self-reported atropine-related decreases in alertness and efficiency. Following exercise, the subjects reported feeling relatively more alert, refreshed and efficient at each of the three atropine doses. Again, these results do not favor the hypothesis that moderate exercise potentiates the effects of a subsequent dose of atropine.

b.3 Selected physiological variables

In Year 1, exercise caused increased heart rate, reversed the bradycardia associated with the low (0.5 mg) dose of atropine and significantly increased the tachycardia associated with the 1.0 and 2.0 mg doses. Among these effects, perhaps the most interesting is the reversal of the bradycardia found with the low dose of atropine. The slowing of heart rate observed with atropine doses in the clinical range is generally thought to be due to direct central stimulation of vagal nuclei in the brainstem (21). Reversal of this effect by prior exercise might also be mediated by central mechanisms of cardiac control.

c. Effects of sleep deprivation on information processing, self reports and selected physiological measures.

c.1 Information processing

Sleep deprivation is typically thought to induce a general, nonspecific reduction of energy resources, leading to impaired performance. However, recent data suggest that, like atropine, sleep deprivation may selectively impair functions associated with stimulus analysis and identification. For example, Wilkinson and colleagues (25, 26), studying the effects of sleep deprivation on auditory vigilance, found a significant decline in d' but no systematic change in ß. Horne et al. (27) confirmed these

findings. Note, however, that issues recently raised by Naitoh (28) may affect the interpretation of results based on applications of signal detection analysis to vigilance performance. We will address those issues in the Discussion section of this report.

Employing a serial stage theoretical model of information processing, along with Sternberg's (17) additive factor method, Frowein (8) and Sanders et al. (9) found that the effects of sleep state (i.e., normal sleep vs. sleep deprivation) interacted with those of two task-related experimental variables, stimulus quality and time uncertainty on reaction time. The effects of the several task variables among themselves were additive. As indicated earlier, where the effects on choice reaction time of certain rationally selected task variables are found to be additive, serial stage theorists infer that each task variable selectively influences a different stage in the reaction process. Thus signal intensity, signal quality, stimulus-response compatibility and time uncertainty, which usually show additive effects on choice reaction time, are said to influence a stimulus preprocessing stage, a stimulus identification stage, a response selection stage and a response preparation stage, respectively (29). If a new experimental variable such as sleep deprivation or a drug treatment shows hyperadditive interaction effects with one or more of the established task variables, but has additive effects with others, one infers that the new experimental variable and the task-related variable with which it interacts both influence the same stage in the reaction process. Since the effects of sleep deprivation interacted specifically with those of stimulus quality and time uncertainty and not with the effects of other established task variables, Sanders and Frowein and their colleagues concluded that sleep deprivation selectively slows processing in two stages of the reaction process, stimulus identification and response preparation. This hypothesis and these findings lead to the prediction that atropine, which also influences the stimulus identification stage, and sleep deprivation will have hyperadditive interaction effects on performance.

In the Year 2 studies, the effects of sleep loss were as predicted from the report by Wilkinson's group (26) and by Horne and colleagues (27). In the aircraft identification task, a night of sleep deprivation was associated with a significant decrease in hits, an increase in false alarms, a decrease in d' and no systematic change in ß. As reported earlier in this review, the 2.0 mg dose of atropine also reduced d' but had no effect on ß. For the aircraft identification task, the predicted hyperadditive interactions between the effects of atropine dose and sleep loss were not found. This may have been due to "floor" effects in this particular task. That is, when atropine was administered in the combined treatment condition, performance had already been impaired by a night of sleep deprivation. The findings with the aircraft identification task are consistent with the hypothesis that both atropine and sleep loss selectively impair perceptual sensitivity. It is of interest to know whether

such effects are modality specific or whether they can be generalized to the auditory modality. For this and other reasons, we included the auditory vigilance task in the Year 2 test battery. The reader will recall that the stimuli for the auditory task are a randomly ordered series of brief tones composed of five different pitches, the lowest of which is designated the target tone. The subject monitors the stimuli with eyes closed and is instructed to press a designated button as quickly as possible after each target tone and not to respond to the nontarget tones.

The auditory vigilance task showed the same general trends as the aircraft identification task. A night without sleep resulted in significant decreases in hits and in d' and a significant increase in false alarms, with no systematic change in ß. Sleep deprivation had no significant effect on reaction time, probably because the subject received penalty points for response latencies greater that 750 msec. Time on task was associated with a decline in hits and an increase in ß, but d' and false alarms were not affected by this variable. It is surprising that there were no significant sleep loss x time on task interaction effects. The effects of sleep deprivation and time on task are usually found to be hyperadditive (e.g., 29).

The oddity-matching task is a relatively high-speed, information processing task in which reaction time and motor time are the most important response measures. Accuracy is held relatively constant at 90-95% by instructions, practice and feedback. As anticipated from Sanders (29), the effects of sleep deprivation on choice reaction time were considerable increased in the condition of low DSQ. However, the predicted sleep state x TU interaction effect was not found. From a theoretical perspective, the implication of the sleep state x DSQ interaction effect is that one locus of the sleep loss effect is an input processing stage involved in stimulus identification. The sleep loss x TU interaction effect reported earlier by Sanders (29) implied that sleep deprivation also influences a motor adjustment stage in the reaction process. Although we failed to find this interaction effect, sleep deprivation did cause slowing in motor speed. This finding is consistent with the notion that sleep deprivation does influence functions associated with motor adjustment and response preparation.

Sleep state and atropine dose both interact with the task variable DSQ, suggesting that each treatment slows functions associated with stimulus identification. Therefore, one might expect both a significant first-order interaction between these two treatments and a second-order interaction involving DSQ. Statistical analysis of the Year 2 data revealed a significant two-way interaction between the effects of atropine and sleep deprivation on mean reaction time but the tree-way interaction involving DSQ was not significant.

In summary, the results from the analyses of performance data in Year 2 imply that both atropine and sleep deprivation impair

one's ability to selectively attend to and identify task-relevant visual and auditory stimuli. Depending on task requirements, instruction concerning speed and accuracy and feedback to the subject, this impairment may appear as a loss of accuracy or a loss of speed or both.

c.2 Self ratings

Sleep-deprived subjects reported that they felt less able to sustain attention and to think clearly. In addition there were significant atropine dose x sleep deprivation interaction effects on self-reported sleepiness, drunkenness, efficiency, ability think, dizziness and discomfort. Thus, negative self attributions associated with atropine were significantly enhanced in the sleep-deprived state.

c.3 Physiological measures

Sleep deprivation had no systematic effects on heart rate, blood pressure or pupillary size, nor was there evident of any atropine x sleep loss interaction effect. As expected from the work of Carskadon and Dement (5), sleep deprivation did cause a marked reduction in sleep latency (increased sleep tendency) in the multiple sleep latency test. As reported above, atropine dose also caused increased sleepiness. Statistical analyses revealed a significant hyperadditive interaction between the effects of sleep deprivation and atropine on sleepiness, confirming the self-report data.

4. Experimental Methods for Year 3

a. Subjects

Prospective young male subjects were first screened by a semi-structured telephone interview conducted by a senior member of the staff. Callers who reported health problems, drug use or medication use were not admitted to the study. Although no urinalysis was done, each caller was asked whether he would be willing to undergo urinalysis to verify that he was drug free. If he answered, "No," he was not invited to the laboratory.

In a formal assessment at the research center, the volunteer read and signed a consent form and a payment contract, completed the Minnesota Multiphasic Personality Inventory and the Cornell Medical Index and received a standard physical examination conducted by an M.D. He then underwent exercise stress testing, and if he passed all of the screening examinations, he was scheduled for 2 full practice days on the laboratory tasks. Sixty-four volunteers ranging in age from 21 to 35 were entered into the Year 3 research protocol.

b. Research environment

This research was conducted at the Oklahoma Center for Alco-

hol and Drug Related Studies, which is a research unit of the Department of Psychiatry and Behavioral Sciences of the University of Oklahoma College of Medicine. The Principal Investigator is Scientific Director of the Center, which is located in the Rogers Building at 800 N.E. 15th Street, Oklahoma City, on the campus of the University of Oklahoma Health Sciences Center.

c. Experimental design

The design for Year 3 contained two between-group factors, atropine dose (placebo or 2.0 mg atropine sulfate, i.m.) and predose exercise. Sleep state (normal sleep or a night without sleep) was a within-group factor. Paired subjects, one randomly assigned to the atropine dose and the other to a placebo, were entered into the project in either the exercise or the non-exercise condition, which was counterbalanced from week to week. Neither the volunteer nor the technician knew the dose assignment. Subjects began an experimental week at 0800 Tuesday and were practiced for 2 full days to achieve asymptotic performance levels on the laboratory tasks. The subjects were off duty from 1700 Wednesday until they returned to the laboratory Thursday evening for another practice session. Thursday night both subjects either slept (8 hours bedtime) or stayed awake through the night, undertaking the first experimental day on Friday. The subjects were tested before and after the atropine/placebo dose from 0800 to 1700 Friday, after which they left the laboratory to return Sunday Night, either to sleep or stay awake, in preparation for Monday, the second experimental day. The sleep deprivation treatment was counterbalanced from week to week. The 2.0 mg dose of atropine sulfate in a saline vehicle, or the placebo (normal saline) was injected in the thigh, i.m., at about 1200 hours on both Friday and Monday.

Moderate exercise, administered prior to each of the two task cycles on each experimental day, was defined for each subject as exercise that induced 75% of his maximum heart rate. Maximum heart rate had been ascertained during the screening examination in a maximum output treadmill test, using the Bruce protocol (30). Table 1 shows the schedule of activities for a typical experimental day.

d. Performance assessment.

The three performance tasks, aircraft identification, auditory vigilance and oddity matching, were all administered twice daily, once before and again beginning about 1-1/2 hours after injection of 2.0 mg of atropine sulfate or the placebo. The tasks, which are identical to those used in Year 2 of this research, are described briefly below.

d.1 The aircraft identification task

The subject is required to distinguish "friendly" from "enemy" aircraft silhouettes that emerge at random intervals from

Table 1

Typical Schedule for an Experimental Session

(Year 3)

0730	Physiological recording Exercise
0745	Physiological recording Rest
0800	Mood questionnaire Physiological recording Photograph of the eye Sleep latency test
0830	Performance session 1
1000	Photograph of the eye Mood questionnaire Physiological recording Lunch
1130	Physiological recording Exercise
1145	Physiological recording
1200	Injection of atropine sulfate or placebo
1230	Mood questionnaire Physiological recording Photograph of the eye Sleep latency test
1300	Performance session 2
1430	Photograph of the eye Sleep latency test Physiological recording Mood questionnaire
1500	Rest
1700	Escorted home

a background swarm of moving dots. Some of the stimulus events are feints, in which the emerging aircraft turns and recedes into terminate in an aircraft silhouette with a one-inch wingspan. Friendly aircraft have wingtip tanks and enemy craft have tanks near the center line, labeled "cannons." Should the subject fail to press his "fire button" within 700 msec, the enemy cannons fire, illuminating the computer screen with a bright flash. If the subject correctly detects and shoots the enemy aircraft, a yellow "laser" beam intercepts the enemy aircraft and it explodes in yellow. A correct detection (hit) is then recorded. If the subject inadvertently shoots at a friendly aircraft, the aircraft explodes in blue and an error of commission (false alarm) is recorded. The friend/enemy probability is 0.5 and the dependent variables of interest are hits, false alarms, d' and ß. The time on task is 15 minutes.

d.2 Auditory vigilance

The task employs 50-msec tone pips at five different pitches, 850, 1000, 1150,1300 and 1800 Hz, randomly ordered with an interstimulus interval of 2 seconds. The lowest pitched tone is designated as the target event. The subject is required to respond to the target within a deadline of 1 second. Forty-eight targets are presented during each 7.5 minute block and there are 6 blocks per session. The task-related variable "blocks" is used to test for interactions between time on task and the other treatments. The response variables of interest are hits, false alarms, d', and ß. Reaction time is held relatively constant by instructions, feedback and the deadline procedure.

d.3 Oddity matching

This is a 4-choice reaction time task in which the subject is presented with a display of four dials arranged in a square. Each dial has a pointer located at either the 0, 90, 180 or 270 degree radial. On each trial, three of the four pointers are oriented identically, while the fourth is located on a different radial. On half the trails, DSQ is reduced with a random dot mask. On half the trails in orthogonal design, SRC is reduced by a change in the stimulus to response mapping rule. The third task variable, TU, is varied by employing either regular or variable interstimulus intervals. The subject works on a manipulandum containing four response buttons arranged in a square and a center "hold" button. When he has identified the odd dial, he lifts his index finger from the center button (reaction time) and moves his finger a distance of 1 centimeter to the designated response button as quickly as he can (motor time).

e. <u>Self ratings.</u>

The 29 item scale is identical to that used in Years 1 and 2 of this project. It is administered before and after each test cycle.

f. Physiological measures.

The battery of physiological measures is also identical to that employed in year 2. It includes heart rate, blood pressure, pupillary diameter and the multiple sleep latency test. In the latter test, administered after each performance cycle, the subject reclines in a lounge chair and is instructed to go to sleep. One minute of Stage 1 sleep is used to define sleep onset. Heart rate and blood pressure are recorded and displayed with a Critikon Dinamap Vital Signs Monitor manufactured by CRITIKON, Inc, Tampa, Florida, 33622.

5. Results

a. Effects of atropine, sleep deprivation and exercise on information processing.

a.1 Aircraft identification

a.1(a) Effects of sleep state and exercise condition

Table 2 displays means and standard deviations for the several response variables in the aircraft identification task. Note that the columns of scores represent days within exercise condition and within atropine dose and that the major rows represent task cycles within days. For clarity of presentation, the column labeled Day 2 always contains the scores associated with sleep loss. As shown in Table 2, cycle 1 testing occurred prior to the administration of atropine or placebo and cycle 2 occurred about 90 minutes following the injection. In the exercise condition, exercise was scheduled prior to cycle 1 and again prior to drug injection before cycle 2.

To examine performance changes with sleep deprivation, absent any drug effects, consider the cycle 1 scores. Compared to the Day 1 scores, both d' and percent hits decreased on each sleep loss session (Day 2), while percent false alarms increased. Note also small increases in ß on Day 2. For the scores in cycle 1, a 2 (sleep state condition) x 2 (exercise condition) analysis of variance on each of the response variables confirmed significant main effects of sleep state on d', $F = 14.2$, $p < .002$; hits, $F = 15.5$, $p < .001$; and false alarms, $F = 8.3$, $p < .01$. Sleep loss was associated with decreased hits and decreased d' with increased false alarms. There was also a small but significant increase in ß on the sleep loss day, $F = 10.3$, $p < .01$, which failed to replicate in cycle 2, $F < 1.0$. In cycle 1, there were no significant main effects of exercise on any of the response variables but for percent hits, the sleep state x exercise interaction effect was nearly significant at the 0.05 level, $F = 3.9$, $p < .06$. Percent hits decreased when exercise was added to sleep deprivation.

a.1(b) Effects of atropine dose, sleep state and exercise

Table 2
Effects of Atropine, Sleep Deprivation and Exercise
on Aircraft Identification

GROUPS

	Atropine								Placebo							
	EX				NEX				EX				NEX			
	Day 1		Day 2		Day 1		Day 2		Day 1		Day 2		Day 1		Day 2	
	$\bar{X}$	s	$\bar{X}$	s	$\bar{X}$	s	$\bar{X}$	s	$\bar{X}$	s	$\bar{X}$	s	$\bar{X}$	s	$\bar{X}$	s
CYCLE 1																
d'	5.5	0.5	3.7	1.8	5.9	2.2	4.4	2.1	5.3	2.6	4.3	2.4	5.6	2.7	4.5	2.5
H	96.0	9.0	93.1	8.2	98.7	1.7	95.3	5.1	96.9	3.8	91.3	3.8	95.9	6.8	93.9	7.6
FA	6.7	5.3	10.2	6.1	4.5	3.3	7.8	7.1	6.0	5.6	6.5	6.9	7.8	10.8	8.4	12.6
ß	0.4	0.8	0.8	1.0	0.8	1.2	0.9	0.8	0.6	0.6	1.7	1.7	0.7	1.2	1.4	1.5
CYCLE 2																
d'	4.2	2.7	2.2	1.7	4.2	2.4	2.4	0.9	5.1	3.0	3.6	2.0	5.2	2.7	4.8	2.6
H	93.2	10.0	76.6	26.0	94.7	4.6	87.2	9.5	95.3	4.9	91.2	8.5	94.5	9.6	95.3	5.7
FA	9.4	7.5	18.2	13.3	9.5	9.8	15.3	12.5	7.2	7.9	11.2	8.4	6.5	7.1	11.6	13.4
ß	0.7	0.4	0.9	0.5	1.0	1.2	1.1	0.9	1.3	1.5	1.2	1.5	1.0	1.2	1.1	1.6

LEGEND:
Days: 1 = normal sleep; 2 = sleep deprived.
EX = pre-cycle exercise; NEX = no exercise.
Atropine or placebo was administered after exercise, between cycles 1 and 2.
H = percent hits; FA = percent false alarms.

In Table 2 the effects of atropine dose can be appraised by comparing the cycle 1 to cycle 2 scores located in the left half of the table (atropine dose) with those in the right half. Note that in the atropine condition, d' and percent hits decline from cycle 1 to cycle 2, while percent false alarms increases. These trends are particularly marked on Day 2 (sleep deprivation). In the placebo condition the performance scores remain relatively stable from cycle 1 to cycle 2, except for percent false alarms, which increases on Day 2. In 4-way (dose group x exercise condition x sleep state x task cycle) analyses of variance, a significant atropine dose effect for any response variable will appear as a dose x task cycle interaction effect. As would be expected from the scores in Table 3, this 2-way interaction effect was significant for d', $F = 7.2$, $p < .01$; percent hits, $F = 12.2$, $p < .001$; and percent false alarms, $F = 5.3$, $p < .03$.

Table 3

Mean Scores Illustrating Drug Group x Task Cycle Interaction Effects on Response Variables in Aircraft Identification

	SCORE					
	d'		Hits		False Alarms	
Cycle	Atropine	Placebo	Atropine	Placebo	Atropine	Placebo
1	4.9	4.9	95.8	94.5	7.3	7.2
2	3.2*	4.7	87.9*	94.1	13.1*	9.2

* These scores account for the significant first-order interaction effects.

The 4-way analyses of variance also confirmed the significant main effects of sleep state on d', hits and false alarms and confirmed a sleep state x exercise condition interaction effect on percent hits. In the sleep-deprived state, exercise resulted in worse performance than no exercise.

Since atropine and sleep deprivation both have significant main effects on the response variables, it is important to learn whether their effects are additive or hyperadditive. As noted earlier, the changes in scores from task cycle 1 to cycle 2 do

appear to be larger on Day 2, the day of sleep deprivation, particularly for percent hits. A sleep state x drug dose interaction effect would appear in the analysis of variance as a significant 3-way interaction involving sleep state, drug dose and task cycle. This effect was statistically significant for percent hits, $F = 7.7$, $p < .01$, but not for d' or percent false alarms.

In summary, as predicted from the findings in Year 2 of this project and from results reported by other investigators, both a 2.0 mg dose of atropine sulfate and a night of sleep deprivation caused impairment of performance on the aircraft identification task. The response variables d', percent hits and percent false alarms were all sensitive to these treatments, and all three variables showed trends suggesting hyperadditive 2-way interactions between sleep state and atropine dose. However, this interaction effect was statistically significant only for percent hits. In task cycle 1, which took place prior to injection of atropine or placebo, ß, the so-called "caution" statistic in signal detection analysis, showed a small but significant increase during the sleep-deprived state. However, this effect failed to replicate in task cycle 2. The exercise variable was associated with only one significant effect, a 2-way interaction with sleep state such that exercise in the sleep-deprived condition was associated with a further decrease in correct detections. There were no significant main effects of exercise on performance nor were there any interaction effects involving the exercise and drug conditions.

a.2 Auditory vigilance

a.2(a) Effects of sleep state and exercise condition

Statistical analyses indicated that among the several response variables that were assessed in the auditory vigilance task, d' and percent hits were sensitive to the effects of the drug treatment as well as to sleep state and time on task. In order to reduce the complexity of tabular presentation, Table 4 contains means and standard deviations only for d'. As in Table 2, the columns in Table 4 represent days within exercise and drug dose and the major rows represent task cycles within days. Again, the columns labeled Day 2 contain the scores associated with the sleep-deprived state. Between the major rows, trial blocks 1-6 reflect time on task.

To examine the effects of sleep loss, exercise and time on task on d', absent any effects of atropine dose, consider the entries for task cycle 1. Note that in both conditions of exercise, performance declined on Day 2. Note also the general decline in d' with time on task. A 2 (sleep state) x 2 (exercise condition) x 6 (task block) analysis of variance on the d' scores in cycle 1 revealed significant main effects of sleep state, $F = 75.8$, $p < .001$, and time on task, $F = 9.27$, $p < .001$. Exercise had no significant main effect. The first-order interaction of sleep

Table 4
Effects of Atropine Dose, Sleep State, Exercise Condition and Time on Task on Auditory Vigilance (d')

GROUPS

	Atropine								Placebo							
	EX				NEX				EX				NEX			
	Day 1		Day 2		Day 1		Day 2		Day 1		Day 2		Day 1		Day 2	
	$\bar{X}$	s	$\bar{X}$	s	$\bar{X}$	s	$\bar{X}$	s	$\bar{X}$	s	$\bar{X}$	s	$\bar{X}$	s	$\bar{X}$	s
CYCLE 1 Block 1	5.6	2.9	4.5	2.4	6.3	2.9	6.1	2.8	6.7	2.9	4.3	2.1	5.5	2.9	4.8	2.6
Block 2	6.1	2.8	3.7	1.4	6.4	2.4	4.7	1.8	6.6	2.8	4.2	2.2	6.3	2.4	4.1	1.5
Block 3	5.3	2.4	3.1	1.2	4.8	1.7	4.6	2.0	5.4	2.3	3.6	1.6	5.1	2.0	4.0	1.9
Block 4	5.2	2.7	3.0	1.4	5.5	2.3	4.9	1.7	6.6	2.7	3.4	1.8	4.9	2.3	3.9	2.0
Block 5	5.5	2.6	3.1	1.4	5.0	1.8	4.7	1.8	6.2	2.4	4.2	1.8	5.3	2.4	3.7	1.4
Block 6	4.6	2.4	3.9	2.3	5.2	1.5	4.5	1.5	5.3	2.1	4.0	1.5	5.2	2.2	4.2	2.2
$\bar{X}$	5.4	2.5	3.6	1.7	5.6	2.1	4.9	1.9	6.1	2.5	4.0	1.8	5.4	2.4	4.1	1.9
CYCLE 1 Block 1	4.6	2.3	3.6	1.7	5.3	2.4	3.9	2.3	6.1	2.9	4.4	2.3	5.5	2.3	4.1	1.7
Block 2	3.8	2.3	2.6	1.1	4.6	2.1	3.3	1.6	5.9	2.7	3.5	1.6	4.8	2.4	3.8	1.8
Block 3	4.4	2.5	3.2	1.8	5.1	2.3	4.1	1.8	5.2	2.9	3.5	1.7	4.9	1.8	3.4	1.6
Block 4	4.2	2.2	2.5	1.1	3.7	2.0	3.6	1.5	5.3	2.6	3.6	1.6	4.8	2.2	3.6	1.9
Block 5	3.9	1.9	2.5	1.0	4.5	2.5	3.2	2.1	4.5	2.3	3.1	1.4	4.8	2.0	4.2	2.2
Block 6	4.1	2.0	2.6	1.5	4.2	1.6	3.2	1.4	4.9	2.1	3.1	1.4	5.2	2.0	3.7	1.8
$\bar{X}$	4.2	2.2	2.8	1.4	4.6	2.2	3.6	1.8	5.3	2.6	3.5	1.7	5.0	2.1	3.8	1.8

LEGEND:
Days: 1 = normal sleep; 2 = sleep deprived.
EX = pre-cycle exercise; NEX = no exercise.
Block = time on task

state with time on task was also significant, $F = 4.2$, $p < .05$, as was the interaction of sleep state with exercise, $F = 9.7$, $p < .01$. The impairment associated with sleep deprivation increased with exercise and with time on task. There were no other significant interaction effects. Similar analyses for the remaining response variables showed exactly the same pattern of results for percent hits as for d'. Performance declined with sleep deprivation and with time on task and the effects of these treatments were hyperadditive, as were the combined effects of sleep loss and exercise. Percent false alarms showed a significant main effect only of sleep state, increasing in the sleep deprivation condition. The "caution" statistic, ß, showed a small but significant increase with sleep deprivation, $F = 13.8$, $p < .001$, as well as systematic increases with time on task, $F = 11.5$, $p < .001$. The sleep state x time on task interaction effect was not significant for ß and there were no other significant main effects or interaction effects. The significant main effect of sleep state on ß was replicated in task cycle 2, $F = 6.4$, $p < .02$.

a.2(b) Effects of atropine dose, sleep state and exercise

Systematic effects of atropine dose on a response variable in the auditory vigilance task would be found in a significant dose x task cycle interaction effect. In 2 (dose) x 2 (sleep state) x 2 (exercise condition) x 2 (task cycle) x 6 (task block) analyses of variance, this interaction effect proved to be significant for d', $F = 7.5$, $p < .01$, and for percent hits, $F = 18.6$, $p < .001$, but not for percent false alarms, $F = 1.0$, or for ß, $F = 1.2$.

Since d' and percent hits decreased significantly both with sleep deprivation and with atropine dose, it is important to learn whether these treatment effects were additive or hyperadditive. The second-order interaction effect, atropine dose x sleep state x task cycle, was significant for percent hits, $F = 4.4$, $p < .04$, but not for d', percent false alarms of ß. Analyses of simple main effects indicated that this 3-way interaction effect on percent hits was due primarily to a relatively large decrease in hits in cycle 2 in the atropine/sleep deprivation treatment combination. The absence of a significant dose x sleep state interaction effect on d' may have been due to floor effects for that response variable. When atropine was administered in the sleep loss/atropine dose combination, the d' score had already decreased toward zero.

The exercise x sleep state interaction effects found in the analysis of the cycle 1 scores also appeared in the overall analysis. The interaction effect was significant for d', $F = 7.1$, $p < .05$, and for percent hits, $F = 5.2$, $p < .05$, but not for false alarms. Analyses of simple main effects indicated that performance was particularly impaired in the sleep loss/exercise treatment combination. Exercise had no significant main effects on any of the response variables, nor were there any significant exercise x atropine dose interaction effects.

In summary, the results for auditory vigilance were quite similar to those for aircraft identification. A 2.0 mg dose of atropine and a night without sleep each impaired signal detection performance and their effects interacted to cause considerable impairment in one of the several response measures, percent hits. The performance impairments associated with sleep deprivation increased with time on task and also with exercise, but exercise had no significant main effects on performance. As was found with the aircraft identification task, the signal detection variable, ß, showed small but statistically significant increases both with sleep deprivation and with time on task.

a.3 Oddity matching

a.3(a) Effects of sleep state and exercise condition

Table 5 displays means and standard deviations for average reaction times in all treatment combinations for the oddity-matching task. As in the earlier tabular presentations, the major columns show the several combinations of dose, exercise condition and sleep state and the major rows show scores for the two task cycles. The eight rows within each task cycle reflect the treatment combinations related to the three task-related variables, DSQ, SRC and TU. To appraise the main effects of sleep deprivation on reaction time, absent any effects of atropine dose, examine the middle row of Table 5, labeled X$\underline{t}$. Note that overall mean reaction time shows consistent increases on Day 2, the sleep loss session. Analysis of variance of mean reaction times in task cycle 1, based on sleep state, exercise condition and two levels each for the three task-related variables, revealed significant main effects of sleep state, $\underline{F}$ = 21.1, $\underline{p}$ <.001, and of each of the task variables, DSQ, $\underline{F}$ = 706.5, $\underline{p}$ <.001; SRC, $\underline{F}$ = 299.9, $\underline{p}$ <.001; and TU, $\underline{F}$ = 46.0, $\underline{p}$ <.001. There was no significant main effect of exercise, and the exercise x sleep state interaction effect was not significant. As expected from the Year 2 results, the task variable DSQ showed a hyperadditive interaction effect with sleep state such that average reaction time for the sleep-deprived subject was particularly long when DSQ was poor. There was a significant underadditive interaction between the effects of sleep state and SRC such that the effect of SRC was smaller in the sleep deprivation condition than in the normal sleep state. There was no significant sleep state x TU interaction effect.

The analysis of mean motor times in task cycle 1 revealed a significant main effect of sleep loss, confirming results reported for Year 2. In addition, motor time showed significant increases in both the low DSQ and the low SRC conditions. Neither TU nor exercise affected motor time.

a.3(b) Effects of atropine dose, sleep state, exercise condition and the task variables

Table 5
Effects of Atropine Dose, Exercise Condition, Sleep State and Task Variables on Reaction Time

			GROUPS: Atropine								GROUPS: Placebo							
			EX				NEX				EX				NEX			
			Day 1		Day 2		Day 1		Day 2		Day 1		Day 2		Day 1		Day 2	
DSQ	SRC	TU	$\bar{X}$	s	$\bar{X}$	s	$\bar{X}$	s	$\bar{X}$	s	$\bar{X}$	s	$\bar{X}$	s	$\bar{X}$	s	$\bar{X}$	s
CYCLE 1																		
H	H	F	911.0	245.0	902.4	284.3	945.8	261.6	953.7	259.0	846.4	208.3	945.3	220.1	880.8	258.8	858.9	227.6
H	H	V	912.6	245.6	950.3	270.8	988.8	281.2	1003.0	297.4	914.1	243.3	992.7	258.6	889.1	220.7	946.1	246.8
H	L	F	1015.1	296.3	1111.7	349.7	1079.5	308.8	1100.9	319.8	967.5	234.0	1039.5	246.2	1004.3	299.5	1040.0	298.6
H	L	V	1017.3	286.3	1107.6	331.4	1096.6	292.0	1173.9	351.5	985.0	348.1	1095.6	305.8	1013.3	274.4	1074.2	317.1
L	H	F	1410.3	302.2	1442.4	333.5	1379.8	282.2	1432.1	315.4	1298.5	288.9	1439.7	287.1	1298.1	374.0	1413.9	329.0
L	H	V	1445.8	277.8	1517.5	315.2	1485.6	318.8	1481.5	288.6	1371.0	240.8	1503.4	397.5	1399.7	301.6	1538.0	332.2
L	L	F	1538.6	314.5	1735.5	388.0	1633.9	355.8	1689.9	347.0	1424.7	299.9	1587.6	352.6	1565.3	327.7	1676.1	415.3
L	L	V	1599.0	322.3	1760.9	365.6	1725.6	388.0	1763.4	368.7	1534.5	297.0	1691.4	321.2	1612.6	372.9	1672.1	433.3
		$\bar{X}t$	1231.2	286.3	1316.0	329.8	1291.9	311.1	1324.8	318.4	1167.7	257.5	1286.9	286.1	1207.9	291.2	1277.4	325.0
CYCLE 2																		
H	H	F	863.5	224.1	980.8	291.8	858.8	263.9	962.2	306.2	869.8	241.6	926.6	234.8	848.3	325.5	879.2	274.1
H	H	V	967.6	279.5	1018.8	339.4	985.8	280.2	984.0	347.6	902.4	226.6	992.3	260.6	925.6	237.0	944.5	274.9
H	L	F	1038.5	303.7	1126.3	362.8	1046.0	318.7	1202.6	358.2	1031.7	271.5	1118.9	310.2	1023.8	297.8	1037.7	318.6
H	L	V	1031.3	303.2	1192.5	419.5	1115.0	381.2	1164.2	376.1	1037.5	275.6	1139.9	330.4	1005.4	291.1	1057.2	347.7
L	H	F	1453.7	342.8	1669.0	449.0	1382.0	335.1	1528.7	379.8	1333.9	255.1	1497.7	323.5	1442.6	359.9	1452.0	324.1
L	H	V	1550.8	314.0	1738.0	451.5	1481.4	296.2	1497.2	412.4	1421.3	263.0	1508.4	286.8	1522.6	359.5	1530.7	327.6
L	L	F	1559.5	334.4	1883.9	461.6	1676.9	396.0	1823.7	459.1	1546.4	311.2	1642.4	375.0	1586.5	385.0	1680.9	407.7
L	L	V	1664.9	366.0	2076.5	512.0	1728.3	382.3	1806.0	408.1	1576.9	334.6	1754.2	361.3	1616.0	323.8	1736.5	418.8
		$\bar{X}t$	1278.7	314.7	1455.9	411.7	1284.4	331.7	1383.6	380.9	1215.0	272.4	1320.0	310.3	1246.4	311.2	1289.8	336.7

LEGEND:
EX = exercise; NEX = no exercise.
DSQ = display quality; SRC = stimulus response compatibility.
TU = time uncertainty; F = fixed intertrial interval; V = variable intertrial interval.
Day 1 = normal sleep; Day 2 = sleep deprived.
Xt = overall mean reaction time.

A main effect of atropine dose on mean reaction time in the oddity-matching task would appear as a significant dose x cycle interaction effect. In the overall analysis of variance, with the dose conditions and cycle added to the design, the dose x cycle interaction effect was not statistically significant, $F = 2.2$, $p < .15$. However, the second-order, 3-way interaction involving atropine dose, cycle and sleep state was significant, $F = 10.7$, $p < .01$, as was the 3-way interaction involving atropine dose, cycle and DSQ, $F = 5.7$, $p < .05$. Table 6 (a and b) displays these second-order interaction effects. These results confirm those found in Year 2 of this research, showing that atropine caused significant slowing of reaction time only when performance had been degraded, either by loss of sleep or by low DSQ.

The overall analysis of variance found no significant main effect of exercise on mean reaction time but the exercise x sleep state interaction effect was just short of statistical significance, $F = 2.9$, $p < .06$. The slowing of reaction time caused by sleep deprivation tended to increase in the exercise condition.

Atropine dose had no significant main effect on mean motor time, nor did exercise, and there were no significant interaction effects involving atropine dose, sleep state or exercise.

In summary, both mean reaction time and motor time increased significantly with sleep loss and for reaction time there was a significant hyperadditive sleep state by stimulus quality interaction effect. As in Year 2, atropine dose caused significant slowing of reaction time only when performance had been degraded by sleep loss or by low stimulus quality. The exercise variable had no significant main effect on reaction time but did show a borderline 2-way interaction with sleep state. That is, slowing due to sleep loss was most pronounced in the exercise condition.

b. Self reports.

b.1 Effects of atropine dose, sleep state and exercise condition

Before and after each task cycle, each subject assessed his state on a set of 29 pairs of bipolar adjectives, each separated by a 7-point scale. The subject marked a scale interval to indicate his position on dimensions such as alert/drowsy. In the Appendix, Table 1 contains the 29 self-report items as they were presented to the subjects. In Table 2 of the appendix, the items are sorted by content into a priori clusters. The first 5 items concern alertness and sleepiness; items 6 thru 9 inquire about enthusiasm, boredom, involvement and attentiveness; items 10 through 17 concern various aspects of physical and mental efficiency; items 18 through 26 are related to emotional and physical well-being; and the last 3 items refer to autonomic effects commonly associated with atropine. Note that when sleep deprived, our subjects moved their ratings toward the unfavorable pole for nearly all symptoms and states in the list. Clearly the demand

Table 6 (a)

The Second-Order Interaction Effect of Atropine Dose, Sleep State and Task cycle on Mean Reaction Time

	DOSE			
	Atropine		Placebo	
Cycle	SD	NSD	SD	NSD
1	1320	1262	1282	1188
2	1420	1282	1305	1232
Cycle 1 - Cycle 2	100	20	23	43

Table 6 (b)

The Second-Order Interaction Effect of Atropine Dose, Display Quality and Task Cycle on Mean Reaction Time

	DOSE			
	Atropine		Placebo	
Cycle	L-DSQ	H-DSQ	L-DSQ	H-DSQ
1	1565	1017	1502	968
2	1668	1034	1553	983
Cycle 1 - Cycle 2	103	17	51	15

LEGEND:
SD = sleep deprivation.
NSD = normal sleep.
L-DSQ = low display quality.
H-DSQ = high display quality.
cell entries: mean reaction time in msec

characteristics of a night without sleep led to reports of generalized impairment.

In the atropine dose condition and in the exercise condition, subjects were more selective in their choice of descriptors. Those who had received the atropine dose rated themselves as more drowsy, lethargic and passive; less attentive, less efficient, less steady; and slower and weaker. These self assessments in the atropine dose condition are very similar to those reported for Years 1 and 2 of this research. Subjects in the exercise condition rated themselves as less interested, less attentive and less involved than those in the nonexercise condition, as well as less coordinated, less sober, less steady, less healthy, less comfortable, weaker, hotter and more sweaty.

There were no significant interaction effects among the three treatments, and the tendency for exercise to reverse the effects of atropine dose that was observed in Year 1 failed to replicate in Year 3.

c. Effects of atropine dose, sleep state and exercise condition on physiological variables.

c.1 Sleep onset latency

As shown in Table 1, sleep onset latency was measured three times on each experimental day, once prior to atropine or placebo injection, then prior to and again following task cycle 2. Table 7 displays means and standard deviations of sleep onset latencies in the various treatment combinations. As would be expected, the mean sleep latencies shown in the top row (cycle 1) of Table 7 indicate a large main effect of sleep state. Following a normal amount of bedtime, sleep latencies averaged about 12 minutes but following a night without sleep, latency scores averaged about 5 minutes. This effect was statistically significant, $F = 145.9$, $p < .001$. It is no surprise, of course, that sleep deprivation causes a great increase in sleepiness. However, the result is necessary to the validity of the sleep latency test. The column scores for Day 1 indicate large decreases in sleep latency following the dose of atropine, between cycle 1 and cycles 2 and 3, but very little change following the placebo injection. The main effect of dose, exhibited in a dose x cycle interaction effect, was statistically significant, $F = 9.6$, $p < .01$. Note also that despite the powerful effect of sleep deprivation on Day 2, the atropine-associated decrease in sleep latencies (cycle 1 to cycles 2 and 3) on Day 2 appears to be greater than the placebo-related change on Day 1. Table 8 displays the mean sleep latencies reflecting these trends. In Table 8, the trends suggest an interaction effect involving sleep state, dose level and time of day. This 3-way interaction proved to be statistically significant, $F = 6.0$, $p < .05$, a result indicating that the effects of

Table 7
Effects of Atropine Dose, Sleep State, Exercise and Time of Day on Sleep Latency (Min.)

DOSE

	Atropine								Placebo							
	EX				NEX				EX				NEX			
	Day 1		Day 2		Day 1		Day 2		Day 1		Day 2		Day 1		Day 2	
	$\bar{X}$	s	$\bar{X}$	s	$\bar{X}$	s	$\bar{X}$	s	$\bar{X}$	s	$\bar{X}$	s	$\bar{X}$	s	$\bar{X}$	s
CYCLE																
1	12.3	6.5	4.1	2.1	10.7	4.7	4.6	3.9	12.5	5.9	4.3	2.7	12.1	7.4	6.2	5.8
2	5.6	6.3	2.1	1.3	6.0	2.8	3.8	2.5	10.0	5.1	4.1	2.3	13.3	5.9	5.0	4.7
3	3.9	2.4	1.3	0.6	6.6	5.1	3.1	2.7	12.3	6.8	3.7	2.1	13.5	6.6	5.6	6.0

LEGEND:
EX = exercise; NEX = no exercise.
Day 1 = normal sleep; Day 2 = sleep deprived.
Cycle 1 = pre-dose.
Cycle 2 = post-dose, pre-task cycle 2.
Cycle 3 = post-task cycle 2.

atropine dose and sleep state on sleep tendency were hyperadditive. There was no significant main effect of exercise on sleep latencies and there were no significant first- or second-order interaction effects involving exercise.

Table 8

Mean Sleep Latency Scores Reflecting the Second-Order Interaction between the Effects of Atropine Dose, Sleep State and Time of Day

	DOSE			
	Atropine		Placebo	
Cycle	Day 1	Day 2	Day 1	Day 2
1	11.5	4.3	12.3	5.3
2	7.1	3.0	11.7	4.5
3	5.3	2.2	12.9	4.7

LEGEND:
Injection was administered between measurement cycles 1 and 2.

To summarize, both a night without sleep and a 2.0 mg dose of atropine caused significant increases in sleep tendency and the effects of the two treatments were hyperadditive. Moderate exercise administered prior to cycles 1 and 2 of the multiple sleep latency test had no significant effect on sleep tendency nor were there significant interaction effects involving exercise.

c.2 Pupillary diameter

As can be seen in Table 1, the eye was photographed four times on each experimental day, twice before and twice after the injection of atropine or placebo. There were no significant main effects of sleep state or exercise on pupillary size, but, as expected, there was a significant atropine dose x cycle interaction effect, $F = 21.2$, $p < .001$. Table 9 contains the means and standard deviations of pupillary diameter, exhibiting this effect.

Table 9

Effects of Atropine Dose and Measurement Cycle on Pupillary Diameter (mm)

	DOSE			
	Atropine		Placebo	
Cycle	$\bar{X}$	s	$\bar{X}$	s
1	3.4	0.7	3.3	0.6
2	3.4	0.5	3.1	0.5
3	3.8	0.7	3.3	0.5
4	4.1	0.7	3.1	0.4

LEGEND:
The injection was administered between cycles 2 and 3.

c.3 Heart rate

As can be seen in Table 1, there were eight physiological recording cycles on each experimental day. For subjects in the exercise condition, cycles 1 and 2 and cycles 5 and 6 bracketed the exercise periods. Cycles 3 and 4 and cycles 7 and 8 bracketed the two task performance runs. The drug or placebo injection occurred between recording cycles 6 and 7. For clarity of presentation, we report first the effects of atropine dose and sleep deprivation in the nonexercised subjects. As was found in Years 1 and 2, the 2.0 mg dose of atropine caused a sharp increase in heart rate from a baseline average of 68 beats per minute (BPM) to 100 BPM 30 minutes after the injection, subsiding to 75 BPM 2 hours later. Heart rates in the placebo condition averaged about 69 BPM throughout the day. The atropine dose x measurement cycle interaction effect was statistically significant, $F = 19.7$, $p < .001$. The main effect of sleep state on heart rate was not significant nor was the atropine dose x sleep state interaction effect.

Exercise, when added to the research protocol, had large immediate effects, with heart rate increasing from baseline levels of about 70 BPM to post-exercise levels of about 152 BPM. In measurement cycle 3, approximately 30 minutes following the first exercise period, heart rates were still elevated, averaging about

84 BPM, but by measurement cycle 4, 2 hours later, heart rates had returned to baseline levels. In the placebo condition, in cycle 7, about 1 hour following exercise, heart rates remained elevated at about 78 BPM but had returned to baseline levels by measurement cycle 8. Heart rates rose, of course, after the atropine dose and remained high in measurement cycle 7, averaging 104 BPM. The atropine dose x exercise interaction effect was not statistically significant, $F < 1.0$, and there were no significant effects involving sleep state. In summary, both atropine dose and exercise caused large increases in mean heart rate, but their effects were additive. Sleep loss had no effect on heart rate.

c.4 Blood Pressure

Exercise caused an immediate and statistically significant increase in systolic blood pressure from a baseline mean of about 130 mm mercury to 140 mm. Systolic levels returned to baseline in measurement cycles 3, 4 and 5 and in cycles 7 and 8. There were no significant effects of atropine dose or sleep state on systolic blood pressure and there were no significant interaction effects.

In Year 2 of this research, we reported a small but statistically significant atropine dose effect on diastolic blood pressure. The present results exhibit a similar effect as a significant interaction between atropine dose and measurement cycle, $F = 5.8$, $p < .05$. With the atropine dose, diastolic pressure rose from a baseline average of about 78 mm mercury to about 84 mm. Neither exercise condition nor sleep state affected diastolic blood pressure and there were no significant interaction effects among the experimental variables. In summary, exercise caused increases in systolic pressure but had no effect on diastolic pressure. Atropine dose increased diastolic pressure but had no effect on systolic pressure. There were no effects of sleep state of any of the cardiovascular variables and no significant interaction effects among any of the experimental treatments.

6. Discussion

a. Performance measures.

The effects of atropine and sleep deprivation on the three information processing tasks replicate generally our earlier results in Years 1 and 2. The absence of exercise main effects on performance is consistent with the Year 1 data but the hyper-additive exercise x sleep loss interaction effects found in Year 3 were unexpected.

a.1 Atropine dose effects

As had been predicted from our previous results and from work by Wesnes and Warburton (15, 31) and by Calloway (16), the 2.0 mg dose of atropine impaired signal detection performance in the aircraft identification task by decreasing perceptual sensitivity

(d') and not by altering response decision strategies. Hits on enemy aircraft declined, while false alarms (shooting at friendly aircraft) increased. Since subjects in the atropine dose condition do complain of blurred vision, it became important to estimate the degree to which atropine effects in the aircraft identification task resulted from peripheral rather than central impairment of visual functioning. The decrease in d' could have been due either to central effects on visual function or to blurring of vision caused by peripheral defects such as mydriasis or cycloplegia. A series of studies by Baker and colleagues (22) showed that our findings are probably not due entirely to peripheral effects of atropine. Baker et al. (22) found that basic visual functions such as static visual acuity, depth perception, and simple target identification were not affected by a 2.0 (per 70.0 kg body weight) dose of atropine administered to healthy young men. There is other evidence relevant to this question. Wesnes and Warburton (15) found that methscopolamine, a peripheral cholinergic blocker, caused no impairment on a visual vigilance task which had shown scopolamine dose effects. Dunne and Hartley (18) reported that scopolamine impaired the recall of words in dichotic listening tasks, indicating that scopolamine effects were not restricted to the visual modality. In Year 2 of this research program, we added the auditory vigilance task to our test battery. Our findings in the Year 3 investigation confirmed those in Year 2. The atropine dose impaired auditory vigilance performance by decreasing perceptual sensitivity (d') and not by altering response decision strategies. Taken together, the findings summarized above support the conclusion that atropine has selective effects on perceptual functions and that these effects are centrally mediated.

In the oddity-matching task, with reaction time and motor time as the major response variables, the Year 3 results replicated those of Year 2. Atropine dose alone had no significant independent effect on mean reaction time but the drug did produce significant slowing when performance was degraded by low DSQ. This hyperadditive dose x DSQ interaction effect was selective and specific in that atropine dose had simple additive effects with the other two task variables, SRC and TU. The task variable DSQ is targeted on a hypothetical input stage in the reaction process that we have labeled stimulus identification. Taken as a whole, the performance data from our 3 years of research provide firm support for the hypothesis put forth by Wesnes and Warburton (15, 31) and by Calloway (16) that antimuscarinic agents cause impairment of input functions such as stimulus identification and not of output functions such as response selection or response execution.

a.2 Sleep deprivation effects

As reviewed earlier, findings by Wilkinson and his colleagues (25, 26), and by Horne et al. (27), Frowein (8) and Sanders et al. (9) led to revision of commonly held views about the effects of sleep deprivation on performance. These relatively recent

studies support the notion that sleep deprivation has selective effects on specific components of information processing tasks. Thus Wilkinson and his colleagues (25, 26), investigating the effects of sleep loss on auditory vigilance, found declines in d' but no change in ß. Frowein (8) and Sanders et al. (9), using the additive factors method with a reaction time task, found that sleep state interacted with two task-related variables, stimulus quality and time uncertainty, on choice reaction time but had simple additive effects with their other task variables, stimulus intensity and stimulus response compatibility. Those investigators concluded that sleep deprivation caused selective impairment of two stages in the serial stage reaction process, an input stage associated with stimulus identification that they labeled "feature analysis," and an output stage, response preparation.

Our results in Year 2 and again in Year 3 are fairly consistent with those reviewed above. A night of sleep deprivation resulted in decreased hits and increased false alarms in both the aircraft identification task and the auditory vigilance task. These effects resulted in decreased d' scores, supporting Wilkinson's (26, 27) conclusion that sleep deprivation impairs perceptual sensitivity. Unfortunately, our results for the signal detection variable, ß, were not stable from Year 2 to Year 3. In Year 2, sleep loss had no significant effect on ß in either of the two tasks. In year 3, sleep loss resulted in small but statistically significant increases in both tasks. The latter effects raised a question about the interpretation of the sleep loss-related decreases in d' because the rise in ß scores could reflect a general decline in motivation to respond. The use of d' as an index of perceptual sensitivity depends on the assumption that the subject has a steady motivation for work. We should emphasize here that with the sample size of 64 and with sleep deprivation as a within-subjects variable, the research design had considerably greater statistical power than is typical for such research. For example, Horne et al. (27), who found no effect of sleep deprivation on ß, employed only 8 subjects and in our Year 2 studies the sample size was 32. However, despite the statistical power in this study, it is likely that decision strategies could have been held constant by manipulation of incentives.

Naitoh (28) has questioned whether signal detection theory and its associated statistics should ever be applied to vigilance performance of sleep-deprived subjects, pointing out that signal detection analysis is based on the assumption that the subject attends to every stimulus. Boredom, fatigue and lapses into deep drowsiness can result in changes in d' and ß that may have nothing to do with the observer's perceptual sensitivity (d') or response criterion (ß). Naitoh states, "If we are really interested in the effect of sleep loss on d' and ß perhaps the best experimental way will be to test psychophysically well-trained subjects not with a vigilance task, but with a signal detection task." Our auditory task is a typical vigilance task. However, our aircraft identification task seems to qualify as a signal

detection task. Well-trained subjects are required to make a response decision for each aircraft stimulus, the stimuli are equally probable exemplars from two categories (friend or foe) and time on task is relatively short. We agree with Naitoh that the lapses of attention associated with sleep deprivation can create difficulties for the interpretation of statistics derived from signal detection theory. Yet the generalization of sleep loss effects across laboratories and across tasks supports the conclusions offered by Wilkinson and his colleagues.

In the oddity-matching task, the Year 3 results with sleep deprivation replicated those of Year 2. That is, along with a main effect on reaction time, sleep state effects interacted with those of DSQ. Average reaction time for the sleep-deprived subject was particularly long when display quality was poor. As in year 2, there was no significant sleep state x TU interaction effect. The hyperadditive interaction between the effects of sleep state and display quality again confirms the findings of Sanders et al. (9). Taken together, the Year 3 results with the three tasks strongly support Sanders's conclusion that like atropine, sleep deprivation causes selective impairment of cognitive functions associated with stimulus identification. Whether, as Sanders et al. (9,29) concluded, sleep loss selectively influences a motor adjustment stage remains a question. The finding by those investigators of a hyperadditive interaction between sleep state and time uncertainty was not replicated in either Year 2 or Year 3 of this research. However, sleep deprivation resulted in significantly increased motor times in both years. This decrease in motor speed could be due to an effect of sleep loss on functions related to motor adjustment and response preparation.

a.3 Exercise effects

As was found in Year 1 of this research, moderate exercise, administered prior to atropine (or placebo) injection, had no significant effects on any of the performance tests. Thus we have no evidence that exercise alone either benefits or impairs cognitive performance.

a.4 Interaction effects involving atropine dose, sleep state and exercise

Since atropine and sleep deprivation both cause impairment of signal detection performance, it is important to learn whether these effects are additive or synergistic. If the effects of these treatments are hyperadditive, their combination could place the operator at considerable risk for a catastrophic performance breakdown. The results in Year 3 replicated those from Year 2 and were similar for both the aircraft identification task and the auditory vigilance task. Atropine dose showed a hyperadditive interaction with sleep state on one of the three response variables, percent hits. That is, in the aircraft identification task, the dose-related tendency to stop firing at enemy aircraft

was significantly potentiated in the sleep-deprived state. Similarly, the atropine/sleep loss combination caused a considerable increase of errors of omission in the auditory vigilance task. However, for false alarms, d′ and ß, the effects of atropine dose and sleep states were additive.

In the oddity-matching task, the interactions of atropine dose and sleep state with the task variable DSQ imply that both treatments cause slowed performance in an input stage of the reaction process. If atropine and sleep loss influence the same processing stage, their effects on reaction time should show a hyperadditive interaction effect. The significant atropine dose by sleep state interaction effect found in Year 3 replicated the Year 2 findings. Again, as in Year 2, the 3-way interaction involving DSQ, atropine dose and sleep state was not statistically significant. This absence of a significant second-order interaction effect suggests a more complex state of affairs than is usually considered in serial state theoretical models of reaction time. That is, although both treatment variables influence functions in an encoding stage of the reaction process, they may influence different functions located in that stage. For example, atropine might affect basic "computational processes" (9) involved in stimulus identification. On the other hand, sleep loss might impair or alter effort mechanisms that mediate the effective mobilization and deployment of energetical resources that serve selective attention. Either effect could cause slowing in a stimulus identification stage. The possibility that both atropine and sleep loss impair the active analysis of input but that they do so via different mechanisms could be tested empirically. Thus if sleep loss affects an effort mechanism required to coordinate and regulate energetical resources, while atropine directly affects computational processes, enhancement of effort by financial incentive might reverse the effects of sleep loss but not those of atropine. Further, if reduced energetical resources can, for the short term, be compensated by extra investment of effort, one should expect the commonly observed sleep state x time on task interaction effect found in Year 3. The additive relationship between atropine dose and time on task, found in both Year 2 and Year 3, is also consistent with the notion that atropine and sleep loss influence different functions in a stimulus identification stage.

Moderate exercise had no significant main effects on any response variable in any of the three performance tasks and there were no significant exercise x atropine dose interaction effects. However, sleep state x exercise interaction effects were statistically significant for d′ and percent hits in both the visual and auditory signal detection tasks and borderline ($p = .06$) for reaction time in the oddity -matching task. In each case, the impairment due to sleep deprivation increased in the exercise condition. These trends were opposite to our tentative predictions. We had expected that moderate exercise would produce general physiological activation, leading to improved performance by the sleep-deprived subjects, at least, over the short term.

b. Self reports.

The self assessments associated with atropine dose were very similar to those reported in Year 1 and Year 2 of this research. Following atropine injection, subjects rated themselves as more drowsy, lethargic and passive, less attentive, less efficient, less steady, slower and weaker. However, the effects of exercise and of sleep loss on self assessments that were reported in Years 1 and 2 failed to replicate in Year 3. For example, in Year 1, exercise tended to reverse the effects of atropine dose so that at the 2.0 mg dose, exercised subjects reported less drowsiness, lethargy and inefficiency than they had reported in the no-exercise condition. In Year 3, subjects in the exercise condition rated themselves less interested, less involved as well as less steady, less healthy, less comfortable and weaker than subjects in the non-exercise condition. In Year 3, the items by which subjects characterized the post-exercise state showed little overlap with those that characterized the atropine state, implying a degree of specificity for those characterizations. We should note that regarding exercise effects, the Year 3 results probably have higher validity than the Year 1 results. In Year 1, the exercise condition was run after a complete dose-response atropine study, employing the same subjects. Thus the exercise condition was confounded with time in the project.

Unfortunately, the implication suggested above that the Year 3 data may have greater internal validity than the Year 1 data tends to be countered by the fact that in Year 3,the self assessments associated with sleep loss are clearly not valid. In the sleep-deprived state, subjects gave negative self assessments for nearly all of the 29 items of the questionnaire. Demand characteristics, inadvertently introduced into the experimental protocols, are the most likely cause of this behavior.

c. Physiological variables.

c.1 Sleep onset latency

During all 3 years of this research, subjects injected with atropine have reported reduced alertness and increased sleepiness. In Year 2, in order to examine the validity of these complaints, we introduced the multiple sleep latency test of Carskadon and Dement (5), a measure of sleep tendency. Several times a day, the subject, wearing EEG leads, is permitted to recline in a quiet, darkened, temperature-controlled bedroom and instructed to go to sleep. Sleep latency (up to 20 minutes) is taken as the time between the instruction to go to sleep and onset of the first minute of stage 1 sleep. The multiple sleep latency test is a direct and extremely sensitive index of sleepiness. For example, Carskadon and Dement (5) have found the test sensitive to loss of as little as 2 hours' sleep. As far as we know, none of the performance tests shown to be valid indicators of drowsiness are sensitive to 2 hours of sleep loss. The Year 3 results

replicated the Year 2 findings, showing that 2.0 mg of atropine caused significant reductions in sleep onset latency, i.e., increased sleepiness, thus confirming the self report data. As expected, sleep deprivation caused a dramatic increase in sleep tendency. However, the decrease in sleep latency associated with sleep loss was not so great as to mask a significant atropine dose x sleep state interaction effect. When instructed to go to sleep, sleep-deprived subjects, given 2.0 mg of atropine, went to sleep almost immediately. This hyperadditive interaction effect, when considered with the performance data reviewed above, suggests that the cholinergic arousal system is directly involved in the induction of sleep.

We had anticipated that moderate exercise might reverse the effects of a night without sleep, activating the subject and reducing sleepiness. However, exercise had no main effects on sleep latencies and there were no significant interaction effects involving exercise.

c.2 Pupillary diameter

As anticipated, the 2.0 mg dose of atropine caused a significant increase in pupillary diameter in all 3 years of this research. Neither sleep state nor exercise condition affected pupillary diameter, nor were there any significant interaction effects involving sleep state or exercise.

c.3 Heart rate

As expected, the 2.0 mg dose of atropine caused a sharp increase in heart rate in all 3 years of these studies. Exercise, added to the research protocol, also caused large increases in heart rate but the effects of exercise and atropine were generally additive. Sleep deprivation had no effects on heart rate and there were no interaction effects involving sleep state.

c.4 Blood Pressure

In both Year 2 and Year 3 of this research, the 2.0 mg dose of atropine caused a statistically significant effect on diastolic blood pressure, with no significant effect on systolic pressures. Following the atropine dose, diastolic pressure rose from a baseline average of about 78 mm mercury to about 84 mm. Exercise caused an immediate and statistically significant increase in systolic blood pressure from a baseline mean of about 130 mm mercury to about 140 mm. Sleep loss had no effects on blood pressure and there were no significant interaction effects among any of the experimental treatments. The absence of significant atropine x exercise interaction effects is not surprising, of course, since their mechanisms of action on the cardiovascular system are different. The increase in heart rate with exercise is due to direct sympathetic stimulation and the increase in systolic blood pressure is probably secondary to the increase in cardiac rate and contractility. In healthy young men, aerobic

exercise also causes vasodilation in skeletal beds, tending to prevent any rise in diastolic pressure. Cholinergic blockade by atropine causes reduced vagal inhibition of heart rate, resulting in large increases in heart rate. As found here, these effects can be accompanied by significant increases in diastolic pressure.

In summary, the results in Year 3 generally replicated those in Years 1 and 2 of these studies, showing that a 2.0 mg dose of atropine impairs cognitive functions associated with the processing of information input in both visual and auditory tasks, but does not affect functions associated with output processes. Thus, depending on instructions and on such task management variables as deadline procedures, atropine causes either slowing or inaccuracy in the active analysis of input. These findings confirm predictions made from the studies of scopolamine effects conducted by Warburton and his colleagues (11, 12) and also by Calloway (16). Those predictions were based on the hypothesis that the central cholinergic activating system mediates the identification and selection of task-relevant stimuli and that its blockade by muscarinic antagonists should result in impaired signal processing. The results reported here are entirely consistent with that hypothesis.

The effects of sleep loss on human performance have usually been viewed as due to a general reduction in arousal (e.g., 32). Reduced arousal should lead to rather general impairments of performance, with more difficult tasks showing greatest impairment. It can be argued that degraded signals and incompatible stimulus response mappings constitute more difficult conditions than undegraded signals and compatible stimulus response connections. In that case, the hypothesis that sleep loss is associated with a general reduction in arousal predicts that performance impairments caused by sleep deprivation should increase by about the same amount for either low DSQ or low SRC. The outcome reported by Sanders et al. (9) was not compatible with that traditional view. Sleep loss showed specific hyperadditive interaction effects with two task-related variables affecting reaction time, stimulus quality and time uncertainty, but had additive relationships with two other task-related variables, stimulus intensity and stimulus response compatibility. Sanders et al. (9) concluded that sleep loss causes selective impairment of two cognitive functions necessary to the reaction process, active analysis of information input and maintenance of a preparatory response set. Our results from both Year 2 and Year 3 generally support the view that sleep loss, like atropine, impairs both visual and auditory input processing. The significant atropine x sleep loss interaction effects found on several response measures implies that the two treatments influence the same stage of the reaction process. However, the predicted sleep state x time uncertainty interaction effect was not found in either year. Thus we were unable to confirm Sanders's (9) conclusion that sleep loss also impairs one's ability to maintain a preparatory response set.

Prior studies in rodents (10) led to the prediction that moderate exercise administered shortly before atropine injection would potentiate the effects of atropine on subsequent performance. This prediction was not confirmed, either in Year 1 or Year 3. Exercise had no main effects on the performance tasks and showed no significant interactions with atropine dose. On the other hand, exercise did potentiate the deleterious effects of sleep deprivation on performance on all three of the tasks used in Year 3. We had guessed that the activating effects of exercise might counter the dearousing effects of sleep loss, producing at least temporary improvement in performance, but this did not occur.

In each year of this research,self reports indicated atropine-related decreases in alertness, efficiency, clarity of thinking, steadiness, and speed. Data from Year 1 suggested that moderate exercise could counter the self-reported atropine effects on alertness and efficiency. However, this finding was not replicated in Year 3. For sleep loss effects, the self-report data from Year 3 were uninterpretable. Following a night without sleep, the subjects endorsed the negative side of all but 1 or 2 of the 29 bipolar adjectives in the questionnaire.

The multiple sleep latency test which was introduced in Year 2 of this research proved to be a valid index of the effects of atropine and sleep deprivation, alone and in combination. A hyperadditive dose x sleep state interaction effect on sleep latency suggests that cholinergic mechanisms may be directly involved in the initiation and maintenance of sleep. It is likely that the excessive daytime sleepiness caused by the atropine/sleep loss combination would eventually lead to catastrophic performance failures in the field.

As expected from an extensive literature, the 2.0 mg dose of atropine produced tachycardia and pupillary dilation. In both Year 2 and Year 3, atropine also caused a rather large and statistically significant increase in diastolic blood pressure, with no dose-related effect on systolic pressure. Moderate exercise caused large increases in heart rate, accompanied by increased systolic blood pressure and no change in diastolic pressure. Sleep loss had no effects on any of the autonomic variables, nor were there any significant interactions among the three treatments.

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APPENDIX

Table 1

Self-Report Form

1.	Active	___/___/___/___/___/___/___/	Passive
2.	Confused	___/___/___/___/___/___/___/	Clear Thinking
3.	Cold	___/___/___/___/___/___/___/	Hot
4.	Awkward	___/___/___/___/___/___/___/	Coordinated
5.	Enthusiastic	___/___/___/___/___/___/___/	Bored
6.	Worried	___/___/___/___/___/___/___/	Confident
7.	Excited	___/___/___/___/___/___/___/	Calm
8.	Alert	___/___/___/___/___/___/___/	Drowsy
9.	Energetic	___/___/___/___/___/___/___/	Lethargic
10.	Efficient	___/___/___/___/___/___/___/	Inefficient
11.	Apathetic	___/___/___/___/___/___/___/	Interested
12.	Sad	___/___/___/___/___/___/___/	Happy
13.	Tense	___/___/___/___/___/___/___/	Relaxed
14.	Dreamy	___/___/___/___/___/___/___/	Attentive
15.	Clear Vision	___/___/___/___/___/___/___/	Blurred Vision
16.	Dizzy	___/___/___/___/___/___/___/	Steady
17.	Involved	___/___/___/___/___/___/___/	Uninvolved
18.	Suspicious	___/___/___/___/___/___/___/	Trusting
19.	Impatient	___/___/___/___/___/___/___/	Patient
20.	Dull	___/___/___/___/___/___/___/	Sharp
21.	Strong	___/___/___/___/___/___/___/	Weak
22.	Fast	___/___/___/___/___/___/___/	Slow
23.	Awake	___/___/___/___/___/___/___/	Sleepy
24.	Hostile	___/___/___/___/___/___/___/	Friendly
25.	Healthy	___/___/___/___/___/___/___/	Sick
26.	Sober	___/___/___/___/___/___/___/	Drunk
27.	Comfortable	___/___/___/___/___/___/___/	Uncomfortable
28.	Refreshed	___/___/___/___/___/___/___/	Weary
29.	Sweaty	___/___/___/___/___/___/___/	Dry

Headache	_____	Numbness	_____	Other_____	
Shakiness	_____	Tingling	_____	_____	
Faintness	_____	Nausea	_____	_____	
Heart Racing	_____	Breathing Problems	_____	_____	
Dry Mouth	_____	Blurred Vision	_____	_____	

APPENDIX

Table 2

Effects of Atropine Dose, Exercise Condition, and Sleep State on Self-Ratings

Item	Atropine				Placebo				Effects (p)		
	EX		NEX		EX		NEX				
	D1	D2	D1	D2	D1	D2	D1	D2	Dose	Ex	SP
1 Alert/Drowsy											
Pre-drug	3.1	5.0	2.8	4.9	3.0	4.7	2.5	4.3	.04	---	.0001
Post-Drug	4.0	5.5	3.9	5.4	3.4	4.4	2.9	4.3			
2 Active/Passive											
Pre-drug	3.2	4.6	2.5	3.8	3.2	4.1	3.2	4.2	.002	---	.0001
Post-drug	4.1	5.0	3.2	4.6	3.6	3.9	4.0	3.9			
3 Energetic/Lethargic											
Pre-drug	3.3	5.0	2.7	4.5	3.2	4.4	2.7	4.3	.006	---	.0001
Post-drug	3.8	5.1	3.5	4.9	3.6	4.3	2.9	3.7			
4 Awake/Sleepy											
Pre-drug	2.8	5.3	2.8	5.3	3.1	4.6	2.5	4.4	---	---	.0001
Post-drug	3.6	5.4	3.5	5.3	3.2	4.8	2.7	3.9			
5 Refreshed/Weary											
Pre-drug	2.8	5.3	2.8	4.7	3.1	4.8	2.2	4.5	---	---	.0001
Post-drug	3.8	5.3	3.5	5.1	3.6	4.9	2.9	4.2			
6 Enthusiastic/Bored											
Pre-drug	3.5	4.7	3.3	4.4	3.6	4.1	3.0	3.9	---	---	.0001
Post-drug	4.1	4.6	4.2	4.6	3.7	4.1	3.2	3.6			
7 Apathetic/Interested											
Pre-drug	5.1	4.4	5.9	5.3	5.2	4.4	5.9	5.5	---	.0006	.0001
Post-drug	4.9	4.1	5.5	4.9	4.9	4.7	5.7	5.4			
8 Dreamy/Attentive											
Pre-drug	5.2	3.8	5.7	4.2	5.0	3.9	4.7	4.9	.02	.01	.0001
Post-drug	4.8	3.4	4.9	3.9	5.0	4.0	5.6	4.9			
9 Involved/Uninvolved											
Pre-drug	2.6	3.5	2.0	3.2	2.8	3.1	2.4	2.6	---	.005	.0001
Post-drug	3.4	4.4	2.5	4.3	3.1	3.3	2.5	2.7			
10 Awkard/Coordinated											
Pre-drug	5.7	4.4	6.2	5.2	5.2	4.6	6.2	5.1	.0001	.001	.0001
Post-drug	4.7	5.0	5.4	4.4	5.1	4.6	6.1	5.3			
11 Efficient/Inefficient											
Pre-drug	2.7	4.0	2.3	3.7	2.7	3.9	2.0	3.9	.004	---	.0001
Post-drug	3.4	4.1	3.0	3.8	3.0	3.7	2.4	3.3			
12 Confused/Clear											
Pre-drug	5.8	4.8	6.2	5.3	5.8	5.0	6.3	5.3	.02	---	.0001
Post-drug	5.0	4.5	5.4	4.6	5.4	4.8	6.0	5.4			
13 Sober/Drunk											
Pre-drug	1.6	2.2	1.3	1.3	1.4	1.8	1.1	1.3	.0003	.002	.0001
Post-drug	2.3	2.7	1.6	2.0	1.5	2.2	1.2	1.8			
14 Dizzy/Steady											
Pre-drug	5.7	4.7	6.4	5.5	5.3	4.8	6.6	5.6	.0001	.001	.0001
Post-drug	4.8	4.4	5.5	4.6	5.4	5.1	6.2	5.6			

APPENDIX, Table 2 (continued)

Item	Atropine				Placebo				Effects (p)		
	EX		NEX		EX		NEX				
	D1	D2	D1	D2	D1	D2	D1	D2	Dose	Ex	SP
15 Dull/Sharp											
Pre-drug	5.5	4.4	5.8	4.5	5.4	4.3	6.0	4.6	---	---	.0001
Post-drug	5.0	4.1	5.3	4.4	5.5	4.4	5.9	4.7			
16 Strong/Weak											
Pre-drug	2.6	4.2	2.0	3.2	2.8	3.7	2.1	3.0	.004	.0003	.0001
Post-drug	3.2	4.8	2.5	3.6	2.9	3.7	2.2	2.6			
17 Fast/Slow											
Pre-drug	3.0	4.5	2.7	4.2	3.2	3.8	2.8	3.7	.03	.03	.0001
Post-drug	3.8	4.0	2.5	4.2	3.1	3.9	2.6	3.3			
18 Worried/Confident											
Pre-drug	5.7	5.0	5.7	5.4	5.7	5.3	6.3	5.8	---	---	.0001
Post-drug	5.2	5.0	5.6	5.1	5.3	5.4	6.1	5.6			
19 Excited/Calm											
Pre-drug	4.9	4.9	4.7	5.4	4.8	4.9	4.7	5.1	---	---	.0001
Post-drug	4.7	5.2	4.9	5.4	4.6	5.1	4.9	5.1			
20 Sad/Happy											
Pre-drug	5.7	4.9	5.8	5.3	5.3	4.9	6.0	5.5	---	.02	.0001
Post-drug	5.2	4.8	5.8	5.0	5.4	4.0	5.7	5.5			
21 Tense/Relaxed											
Pre-drug	5.5	5.0	5.6	5.1	5.2	5.3	5.5	5.5	---	---	---
Post-drug	5.1	5.1	5.6	5.0	5.1	5.4	5.6	5.3			
22 Suspicious/Trusting											
Pre-drug	5.7	5.3	5.7	5.8	5.8	5.5	6.1	5.6	---	---	.01
Post-drug	5.4	5.2	5.4	5.6	5.7	5.7	6.1	5.9			
23 Impatient/Patient											
Pre-drug	5.4	4.4	5.4	4.9	5.0	5.0	5.8	5.2	---	---	.0003
Post-drug	5.5	4.8	5.1	4.9	5.0	5.0	6.1	5.4			
24 Hostile/Friendly											
Pre-drug	6.0	4.9	6.1	6.0	6.0	5.5	6.3	5.9	---	---	.0001
Post-drug	5.5	5.4	5.7	5.7	5.9	5.6	6.2	5.8			
25 Healthy/Sick											
Pre-drug	2.1	3.0	1.7	1.8	1.9	2.7	1.6	1.9	---	.0003	.0001
Post-drug	2.4	3.4	1.8	2.1	1.8	2.6	1.6	1.9			
26 Comfortable/ Uncomfortable											
Pre-drug	2.5	3.4	2.0	2.5	2.4	2.9	1.8	2.8	---	.009	.0001
Post-drug	2.8	3.9	2.2	2.8	2.5	3.1	2.0	3.1			
27 Cold/Hot											
Pre-drug	3.9	4.0	3.7	3.1	3.8	4.0	3.3	3.4	---	.007	---
Post-drug	4.7	4.1	3.8	3.4	4.1	4.0	3.8	3.9			
28 Sweaty/Dry											
Pre-drug	4.8	4.5	6.1	6.0	4.8	4.5	5.1	5.8	---	.0003	---
Post-drug	5.3	5.3	6.4	6.0	5.0	5.0	5.1	5.2			
29 Clear Vision/ Blurred Vision											
Pre-drug	2.6	3.1	2.1	3.3	3.0	3.4	1.8	2.7	.0001	---	.0001
Post-drug	3.4	4.1	3.7	4.3	2.7	3.3	1.7	2.7			

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